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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/659,467

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Michael J. Welsh

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EXAMINER

WEGERT, SANDRA L

ART UNIT

PAPER NUMBER

1646

NOTIFICATION DATE

DELIVERY MODE

08/20/2009

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patatty@ipmvs.com

Office Action Summary	Application No. 10/659,467	Applicant(s) WELSH ET AL.	
	Examiner SANDRA WEGERT	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 April 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-31 is/are pending in the application.
- 4a) Of the above claim(s) 5-23 and 26-29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 24, 25, 30 and 31 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10 September 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1647

Detailed Action

Status of Application, Amendments, And/Or Claims

In view of the Appeal Brief filed on 20 April 2009, PROSECUTION IS HEREBY REOPENED.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below.

Claims 1, 24 and 25 were amended by applicants after Final Rejection (4 November 2008). Claims 5-23 and 26-29 are withdrawn. It should be noted that Claim 4 has an incorrect status identifier. It was labeled as "withdrawn" in the amendment of 4 November 2008, but in fact is an "original" claim and will be examined as such.

Claims 1-4, 24, 25, 30 and 31 are currently under examination.

Claim Objections/Rejections

Claim Rejections-35 U.S.C. § 112, First Paragraph - Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating post-traumatic stress disorder or conditioned fear responses using the means of injecting the ASIC antagonist PcTx directly into the brain, does not reasonably provide enablement for methods of treating post-traumatic stress disorder that involve use of other ASIC channel antagonists, or that involve routes of administration other than ICV injections into the brain, or that involve disorders unrelated to conditioned fear responses. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

As explained in the Advisory Action (4 December 2008), recent evidence submitted by applicants (Coryell, et al, 2007, Biol. Psychiatry 62(10):1140-1148, of record) makes it clear that blocking the ASIC1a channel, using psalmotoxin (PcTx) injected directly into the brain, disrupts or reverses fear conditioning in mice. Since PTSD is one example of fear conditioning, it follows that PcTx could be used to treat the disorder in human beings, provided it was administered in the same way. Applicants argued against the Lack of Enablement rejection in the Appeal Brief

Art Unit: 1647

submitted 20 April 2009, as presented in the Final Rejection (20 August 2008). However, the Enablement rejection, as it pertains to claims 1-4, is now a matter only of *Scope*.

In the interest of clarity, the basis of the rejection is set forth here:

The claims recite a method of treatment for post-traumatic stress disorder or other anxiety disorders, by administering an ASIC ion channel antagonist. Dependent claims list disorders other than PTSD in which anxiety may play a role, and several routes of administration. The specification lays out experiments in which it was shown that ASIC knockout mice show mild deficits in learning a conditioned fear response (see Figure 8), although it was not definitively established if it was generalized anxiety that was lower in these animals, or the ability to learn (or unlearn) a response to novel stimuli. Nonetheless, applicants submitted a recent reference in which experiments were performed in which ASIC receptors were inhibited or antagonized in mice by adding the spider venom psalmotoxin (PcTx) directly into the brain (Coryell, 2007, submitted with Appeal Brief filed 20 April 2009). Single injections of psalmotoxin had no behavioral effects on normal mice, but did inhibit conditioned fear responses in mice undergoing a variety of standard tests of conditioned fear. For example, psalmotoxin inhibited the startle responses of mice conditioned to display fear in response to predator odor (see Coryell, 2007, Figure 1, for example). This is in keeping with applicants' own data which showed staining for ASIC channels in the brain's locus of conditioned fear responses: namely, the amygdala. In addition, applicants performed some in vitro experiments in which ASIC channels were inhibited by adding the sodium channel pump inhibitor amiloride. In addition, as mentioned above, ASIC receptor knockout mice were produced that had mild deficits in tests of classical conditioning and fear conditioning (Specification, Figure 8). The deficits were considered mild based on the

Art Unit: 1647

fact that they could be overcome with increased training or stronger stimuli (page 34, Specification). Applicants demonstrated deficits in the animals in terms of some cranial nerve reflexes and spatial memory, which is in keeping with the demonstrated locations of ASIC receptors in hippocampus, brainstem and cerebellum, as well as the amygdala (Wemmie, et al, 2002, Neuron, 34: 463-477, of record). Thus, Coryell (2007) ties together the techniques used in the instant specification with a method of inhibiting conditioned fear responses, as well as provides a powerful and specific antagonist for ASIC in the form of psalmotoxin.

In summary: the instant Application does not reasonably provide enablement for a method of treating an anxiety disorder such as PTSD by administering an antagonist of the ASIC receptor *other than psalmotoxin*, and by means of any other technique than direct *intracranial* administration (since PcTx does not cross the blood-brain barrier, or is metabolized very quickly, see Escoubas, 2004, p. 557, last paragraph, of record).

Applicants discuss the claim rejections in terms of a *lack* of enablement as put forth in the final rejection (20 August 2008). However, the examiner agrees that the specification, in light of recent research by Coryell, et al (2007), is enabling for treatment of conditioned fear responses by means of injecting PcTx directly into mammalian brain. It is not enabling for treatment of non-conditioned fear states, or those not involving the amygdala, or for using antagonists other than PcTx, or for routes of administration besides ICV.

Due to the large quantity of experimentation necessary to treat an anxiety disorder such as PTSD using ASIC receptor antagonists other than PcTx, or using routes of administration

Art Unit: 1647

besides ICV, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, and the breadth of the claims--undue experimentation would be required of the skilled artisan to make and/or use the claimed invention *in its full scope*.

Claim Rejections-35 U.S.C. § 112, First Paragraph - Lack of Enablement

Claims 24, 25, 30 and 31 are rejected under 35 USC 112, 1st paragraph, for total lack of enablement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants are not enabled for a method of treating a disease state *associated with increased pH* by administering an ASIC channel antagonist.

The instant Application does not reasonably provide enablement for a method of treating disease states associated with a change in pH by administering an ASIC antagonist without confirming that the diseases embraced by the claims involve a change in pH as well as the ASIC receptor. No data are presented in the Specification in which a naturally-occurring disease state is studied as far as the role of pH and as to the involvement of the ASIC channel in the pH change. Furthermore, the specification gives examples in which ASIC channels are studied *in vitro* or in which ASIC knockout mice had certain deficits in learning fear conditioning. However, none of the experiments measured the pH of tissue in which ASIC channels are expressed. No nexus was made between the measured pH of brain regions involved in fear conditioning, the conditioned responses of the animals, and the ASIC channels. Although

Art Unit: 1647

experimentation is not required for a method of treatment, the instant specification and the art do not even hint at a nexus among all three factors of 1) pH, 2) the ASIC receptor and 3) a disease state.

35 USC § 112, first paragraph - Written Description.

Claims 1-4, 24, 25, 30 and 31 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is now based on the fact that applicants were not in possession of an adequate number of compounds that specifically inhibit ASIC1a to be used in the claimed methods, since only one specific compound has been disclosed and the claims read on any compound that inhibits ASIC1.

Claims 1-4, 24, 25, 30 and 31 are directed to methods of treating an anxiety disorder, such as PTSD, by inhibiting ASIC channels. Dependent claims recite pharmaceutical compositions comprising the ASIC receptor antagonist, as well as several routes of administration of the composition. The Specification as filed describes several experiments that confirm the role of the ASIC1 receptor in conditioning and short-term memory. The Specification also discusses the possible cellular relationship between ASIC channels, pH and GABA-A receptors (Specification, page 2). However, the specification does not teach specific ASIC antagonists that can be used for the claimed methods, other than the one example of psalmotoxin (PcTx) provided by Coryell (2007) and that of amiloride, which is a non-specific sodium pump inhibitor (Brief, p. 8).

Art Unit: 1647

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*” (See page 1117). The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed” (See *Vas-Cath* at page 1116).

With the exception of the compound described above, the skilled artisan cannot envision the compounds used for the method of treating an anxiety disorder by administering an ASIC antagonist. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the methods claimed. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of use. The therapeutic products for the claimed methods are themselves required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Applicants have not even disclosed any structural requirements that would be necessary in a genus of ASIC antagonists.

Therefore, only psalmotoxin used for the claimed methods, but not the full breadth of the claims, meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion

No claims are allowed.

Art Unit: 1647

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Manjunath Rao, can be reached at (571) 272-0939.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

/SLW/

15 August 2009

/Gary B. Nickol /
Supervisory Patent Examiner, Art Unit 1646